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PHASE 3 SUMMARY OF MRID 00094011:

TERATOLOGY STUDY IN RATS

STUDY # 281004

FLUMETRALIN

GUIDELINE REFERENCE:

83-3(A) TERATOGENICITY - RAT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

SCIENCE APPLICATIONS, INC.

LA JOLLA, CALIFORNIA

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

GOOD LABORATORY PRACTICE STATEMENT

Science Applications, Inc. is no longer conducting toxicology business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached pages from the report on this study indicate that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study: Merrill Tisdel

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

R103SJ0917MT

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QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT

STUDY TITLE: Teratology Study of CGA-41065 Technical in Albino Rats

TESTING FACILITY:

Science Applications, Inc.
Division of Toxicology
476 Prospect Street
P.O. Box 1454
La Jolla, CA 92038

SPONSOR NAME AND ADDRESS:

Ciba-Geigy Corporation
P.O. Box 11422
Greensboro, North Carolina
27409

SPONSOR-STUDY NUMBER: 281004

PRINCIPAL INVESTIGATOR:

Stephen B. Harris, M.S.

QUALITY ASSURANCE STATEMENT:

The following statements address the Food and Drug Administration's Good Laboratory Practices (GLP) requirements (CFR Title 21, Chapter I, Part 58 Subpart B, Section 58.35(b)(7)) for final reports.

A. Inspection and Reporting Statement: This study was inspected according to the Quality Assurance Unit's Standard Operating Procedures on the following dates:

Dates of Inspection	Phase of Study	Date Inspection Findings Reported to Principal Invest.	Dates of Management Reports
April 29, 1981	Animal Receipt, Randomization, Identification	May 1, 1981	May 12, 1981
May 4, 1981	Protocol Compliance	May 4, 1981	May 12, 1981
May 6, 1981	Vaginal Smearing	May 6, 1981	May 12, 1981
May 11, 1981	Dose Formulation, Dose Administration, Body Weights	May 11, 1981	May 12, 1981
May 13, 1981	PM Clinical Observations	May 14, 1981	June 19, 1981

QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT
(continued)

Dates of Inspection	Phase of Study	Date Inspection Findings Reported To Principal Invest.	Dates of Management Reports
May 21, 1981	Study Notebook Review	May 22, 1981	June 19, 1981
May 28, 1981	Cesarean Sections	May 28, 1981	June 19, 1981
May 29, 1981	Fetal Dissections	May 29, 1981	June 19, 1981
June 18, 1981	Fetal Head Examinations	June 18, 1981	June 19, 1981
June 29, 1981	Skeletal Examinations	June 29, 1981	July 20, 1981
October 29-30, 1981 November 2, 1981	Raw Data and Draft Report review	November 3, 1981	

B. Compliance Statement:

The study was conducted in compliance with Good Laboratory Practices regulations.

Sharon K. Keener
Sharon K. Keener
Quality Assurance Manager

November 16, 1981
Date

C. Final Report Compliance

The final report was reviewed and found to be in compliance on December 8, 1981.

Sharon K. Keener
Sharon K. Keener
Quality Assurance Manager

December 8, 1981
Date

CGA/SAI 281004

Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

R406MT0628MG

83-3 Teratology Studies

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested.
2. N — At least 20 pregnant animals/dose group for mice, rats or hamsters are available. At least 12 pregnant animals/dose group for rabbits are available (three test groups and control group).
3. Y — At the high dose, overt maternal effects such as slight weight loss are reported (or a limit dose is given, 1,000 mg/kg).
4.* Y — At the low dose, no developmental toxicity is reported.
5. Y — Dosing duration is at least during the period of major organogenesis, but may extend up to one day prior to term.
6.* Y/N — Analysis for test material stability, homogeneity and concentration in dosing medium
7. Y — Individual daily observations.
8. Y — Individual body weights.
9. N — Individual food consumption.
10. Y — Necropsy on all animals
11. Y — Individual uterine examination including number of fetal deaths, early and late resorptions and numbers of viable fetuses per sex.
12. Y — All ovaries examined to determine number of corpora lutea.
13. Y — Individual litter weights and/or individual fetal weights per sex/litter.
14. Y — Individual fetus external examination.
15. Y — Individual fetus skeletal examination for 1/3 to 1/2 of each litter for rodents and all for all rabbits.
16. Y — Individual fetus soft tissue examination.

Criteria marked with a * are supplemental and may not be required for every study.

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IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name: N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine

or

2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine

Common Name: Flumetralin

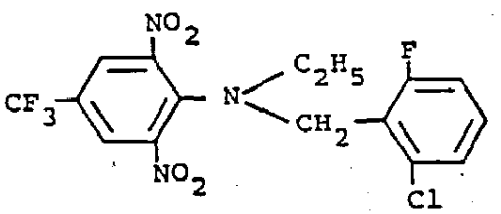
Trade Name: Prime +®

CIBA-GEIGY Code Number: CGA-41065

CAS Registry Number: 62924-70-3

EPA Shaughnessy Number: Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

Flumetralin: 83-3(A): Teratology Study in the Rat

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810009, purity 96.4%.

2. There were 24 female albino rats (CRL:CD(SD)BR) in each of three test groups and a concurrent control. The dose levels were 0 (control), 100, 400, and 800 mg/kg of body weight per day of dosing.

3. There were 20, 19, 21, and 19 litters in the control, 100, 400, and 800 mg/kg/day groups, respectively. One dam in the 100 mg/kg/day group was pregnant but delivered early; the fetuses in this litter were weighed and examined for external changes but were not included in the statistical analyses of the data.

4. Signs of toxicity in the high-dose group included significantly reduced body weight gain (both absolute and percent change) between Days 6 and 20 of presumed gestation.

5. The developmental no-observable-effect level in this study was 800 mg/kg/day, the highest dose tested.

6. The animals were dosed by gavage for ten consecutive days, from Day 6 through Day 15 of gestation (beginning May 11, 1981).

7. Test article/vehicle suspensions were prepared every three days (nine sets of preparations). A sample from each preparation was retained and analyzed for concentration approximately three months after the preparations were mixed. Analytical concentrations averaged 99%, 75%, and 91% of target concentrations for the 100, 400, and 800 mg/kg dosing suspensions, respectively. The dosing suspensions were not analyzed for homogeneity or stability.

8. Dams were observed daily for physical signs and/or general appearance. The only treatment-related observation was dark yellow or yellow-orange urine, and was found in all three test groups during dosing. Other incidental observations included alopecia, opacity of eyes, red staining of eyes, swollen conjunctiva, diarrhea, and bloody discharge.

9. Body weights were recorded on Days 0, 6-15, and 20 of presumed gestation. Body weight gains from Days 6-20 (both

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absolute and percent change) for mid- and high-dose dams were approximately 83% and 85% of control values, respectively. These differences were statistically significant with Dunnett's test at $p < 0.01$.

10. Food consumption was not measured in this study.

11. One dam in the 100 mg/kg/day group was pregnant but delivered early; the fetuses in this litter were weighed and examined for external changes but the dam and litter were not included in the statistical analyses of the data. All other dams were sacrificed on Day 20 of presumed gestation. The thoracic and abdominal cavities were opened and the reproductive organs were examined in situ. The uterus was excised and opened, and the location and distribution of live and dead fetuses and number and type of resorptions were recorded. The only treatment-related finding at necropsy was yellow uterine and periovarian fat in mid- and high-dose dams.

Parameter	Dose Level (mg/kg/day) 0	100	400	800
Total Pregnant Dams (N)	20	20	21	19
Delivered Early	0	1	0	0
On-Schedule Laparohysterectomy	20	19	21	19
Parameters for On-Schedule Laparohysterectomy Dams				
Live Fetuses (mean/litter)	12.4	12.8	12.5	12.4
Live Fetuses (percent)	100.0	100.0	100.0	100.0
Fetal Sex Ratios (% males)	41.7	51.9	45.6	49.6
Resorbed Fetuses (mean/litter)	0.4	0.6	0.6	0.4

12. Ovaries from all animals were examined to determine the number of corpora lutea. There were no differences among the groups in the number of corpora lutea, which averaged 13.5, 14.8, 13.7, and 13.5 in the control, 100, 400, and 800 mg/kg/day groups, respectively.

13. Each apparently viable fetus in each litter was weighed individually. There were no differences among the groups in mean live fetal weights per litter for either males or females.

Sex	Mean Fetal Body Weights (g) Dose Level (mg/kg/day) 0	100	400	800
Males	3.7	3.7	3.6	3.6
Females	3.6	3.6	3.4	3.4

14. Each fetus was examined for gross external abnormalities. Approximately 50% of the fetuses were randomly selected for an examination of the head for internal changes. All fetuses were subjected to a visceral examination. After visceral examination, the fetuses were cleared and stained with Alizarin Red S for skeletal examination.

The litter was used as the unit of analysis, and no significant differences were found for any category of observations, i.e., external, visceral, or skeletal malformations or variations. The most common external malformation was runt, and there were no external variations observed in any group. The only visceral malformations (cardiac/aortic anomalies) were observed in one high-dose fetus; the most common visceral variations were hydroureter and hydronephrosis. The most common skeletal malformations were absence of a rib, one or more vertebrae, or centra. The most frequent variations were the absence of sternebra #5 and the absence or incomplete ossification of sternebra #6. With the absence of conventional signs of embryotoxicity, none of these findings are considered to be biologically significant. Analyses of Bouin's head observations revealed no significant differences among control and treated groups.

15. There were no significant changes from the Acceptance Criteria in this study. Three deviations from the Acceptance Criteria are noted. Under Item 3, two of the test groups (100 and 800 mg/kg/day) had 19 pregnant animals rather than the required 20. Because there were no fetotoxic or teratogenic effects up to and including an MTD and the difference between 19 and 20 is not likely to be consequential statistically, this deviation is considered to be insignificant. Under Item 6, the dosing suspensions were not analyzed for stability or homogeneity. This deviation is considered to be insignificant because (a) stability can be inferred from the concentration analyses which were performed approximately three months after the dosing suspensions were prepared and were found to be generally close to target concentrations; and (b) the procedure of the lab to maintain the dosing suspension on a stir plate during dosing would ensure homogeneity. Under Item 9, food consumption was not measured. This deviation is considered to be insignificant because the dose was administered by gavage, not in the feed. In addition, although there were body weight gain differences in the mid- and high-dose groups, there were no differences in the number or weight of the fetuses, and there were no developmental effects through the highest dose tested.

GILLIS:R515SW0921JG/MT